REMARKS

The only issues outstanding in the Office Action mailed March 17, 2008, is the rejections under 35 U.S.C. § 112 of claims 27 and 28. The Examiner is thanked for indicating that the remaining claims, claims 1-10, 12, 23, 26 and 29-33 have been allowed. It is respectfully submitted that, in view of the following discussion, all claims are in condition for allowance.

Claim 27 has been rejected under 35 U.S.C. § 112, first paragraph. Claim 27 recites a method for treating a primary tumor and/or metastases that are not operatively accessible in a patient, which method comprises administering to the patient and effective amount of a conjugate compound of (allowable) claim 1, said conjugate compound being administered in combination with one or more substances to trigger enhanced cell death and necrosis. It is argued, at page 2 of the Office Action, that the specification enables the one or more substance triggering enhanced cell death and necrosis as L-19 constructs, but nothing else. Applicants respectfully disagree with this analysis. It is argued, at page 3 of the Office Action, that one of ordinary skill in the art "would not have been able to predict which specific substance will have the desired activity." Such a requirement for absolute predictability is not, and has never been, the law. Further, the statement at page 3 of the Office Action that because "there is no way to predict a priori which other substance will be effective in triggering enhanced cell death and necrosis, it would take an enormous amount of trial and error tests [sic, testing of] various substances for their ability to trigger enhanced cell death and necrosis." It is respectfully submitted that the amount of trial and error testing, if such testing is routine, is irrelevant.

In re Wands, discussed at pages 2 through 3 of the Office Action, although not cited, clearly establishes that the *amount* of testing necessary to determine the scope of the claim is not relevant, where such testing is routine. Moreover, *In re Marzocchi,* 439 F.2d 220, 169 USPQ 367 (CCPA 1971), clearly establishes that the mere fact that a claim may be broad, in and of itself, is not dispositive of a lack of enablement.

It is well established that an unsupported suggestion that reactants within a class defined by claims in a typical method of use application would not work, or that such claims embrace inoperative members, insufficient basis alone for rejecting the claims. See *Ex parte Janin*, 209 U.S.P.Q. 761 (POBA 1979). In fact, it is clear that recitations in an Applicants' specification

must be taken by the PTO as an assertion that all compounds encompassed in the claims are operative in the invention, in the absence of reasons or evidence to the contrary. *In re Marzocchi*, supra.

The first paragraph of 35 U.S.C §112 requires only *objective* enablement. Where a specification teaches the manner and process of making and using the invention, the specification *must* be taken as sufficient under §112, unless there is reason to doubt the truth of these statements. See *Marzocchi*, supra. Applicants' specification clearly enables one to identify substances which trigger enhanced cell death and necrosis - several examples are given, and such compounds are further known in the art, beyond the stated examples. One of ordinary skill in the field of pharmacology (and more particularly, in the field of antitumor therapy) is aware that it is the basic goal of a treatment with antitumor agents to increase cell death in neoplastic cells. See, e.g., the disclosure of Remington's Pharmaceutical Sciences, 17th edition, 1985, chapter 63, pages 1139-1140, where it is stated that antineoplastic agents are applied with the intention to kill the tumor cells (page 1140, left column, last paragraph). Moreover, it was commonly known that this effect could be enhanced by combination therapy with two or more antineoplastic agents (see page 1140, right column, second paragraph). Thus, one of ordinary skill reading current claim 27 would immediately understand that the agents suitable for combination with the conjugates of the invention, i.e., substances which trigger enhanced cell death, are antineoplastic agents. Moreover, the skilled artisan would be immediately able to identify compounds having such kind of activity from common general knowledge. Thus, the skilled person would not be confronted with the necessity of open-ended testing to evaluate suitable compounds. (A copy of the citations from *Remington's Pharmaceutical Sciences* is attached herewith.)

On the one hand, it is submitted that the Examiner has not provided any such reasons or evidence to doubt the assertion of utility in the specification and, moreover, breadth of the claims (the only reason given for lack of enablement) does not rise to the level of such reasons or evidence as required by law. As the court stated in *Marzocchi*,

> Turning specifically to the objections noted by the Board as indicated above, it appears that these comments indicate nothing more than a concern over the *breadth* of the disputed term. If we are correct, then the relevance of this concern escapes us. It has never been contended that Applicants, when they included the disputed terms in their

> specification, intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by Applicants that all of the 'considerable number of compounds' which are included in the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics. The only relevant concern of the patent office under these circumstances should be over the *truth* of any such assertion. The first paragraph of §112 requires nothing more than *objective enablement*. How such a teaching is set forth, either by the use of illustrative examples or by broad term analogy, it is of no importance.

Marzocchi, supra. (Emphasis in original.) Thus, the concern expressed at pages 3 and 7 of the Office Action, apparently that the terms used in the claimed methods are broad, does not provide the reasons or evidence necessary by *Marzocchi* to pass beyond the necessity for objective enablement.

Further, in this regard, it is important to note, as a matter of law, that it is not necessary for Applicants' *method* claims to exclude inoperative embodiments, inasmuch as the claims are interpreted in light of the level of understanding one of ordinary skill in the art and, for methods, are interpreted to be *per se* functional. See *In re Angst*, 190 U.S.P.Q. 214 (CCPA 1976) and *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974). These cases state that, for method claims, inoperative embodiments are not encompassed therein and the only questions is whether it would be undue experimentation for one of ordinary skill in the art to determine the scope of the claim. This issue is discussed more fully below. Moreover, anti-tumor utilities are not longer to be considered to be "special", i.e., per se incredulous, by the Patent and Trademark Office. See *Ex parte Rubin*, 5 U.S.P.Q. 2d 1461 (BPAI 1987). As such, applications claiming these methods are, therefore, no more than typical method of use applications wherein the existence of reliable screening protocols correlatable with pharmaceutical activity in humans is sufficient to satisfy § 112, in the absence of reasons to the contrary.

Moreover, it is important to note that a determination of undue experimentation must be considered on a *compound by compound* basis. The mere fact that a claim is broad does *not* mean that it is undue experimentation is required to determine enablement of the compounds therein, if it is not undue experimentation to determine enablement for *each*

compound in the scope of the claim. See, for example, *In re Colianni*, 195 U.S.P.Q. 150 (CCPA 1977). One of ordinary skill in the art can easily determine, what the protocol is given in the specification, whether a given compound has the utility stated. Thus, the mere fact that many compounds must be tested is not dispositive of lack of utility.

Accordingly, since as discussed above one of ordinary skill in the art would be readily able to identify compounds within the scope of the claims, it is submitted that the claim is fully enabled, and withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

Claim 28 has also been rejected under 35 U.S.C. § 112, second paragraph as being indefinite. It is argued, at page 4 of the Office Action, that the claim contains an improper Markush group in that both the EDB fibronectin and the A4 prodrug are L-19 constructs. Regardless, it is submitted that such "double inclusion" is not impermissible in a Markush claim. MPEP § 2173.05(o) expressly addresses this situation, and states that, if a claim is clear, the mere fact that it contains a double inclusion is not dispositive of indefiniteness. In any event, in order to streamline what has already been an extended prosecution, Applicants have reformulated claim 28 into a generic claim, and added new claim 34 directed to the species. It is thus respectfully submitted that this issue is moot.

The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, she is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Harry B. Shubin/
Harry B. Shubin, Reg. No. 32,004
Attorney for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410
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